ORIGINAL ARTICLE

Clinical Profile and Prescription Patterns of Patients with Epilepsy: An experience from Tertiary Care Center.

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ABSTRACT

Background: Newer ASDs (Antiseizure drugs) has changed prescription patterns in India as well as worldwide and it makes choosing appropriate drugs difficult for a different type of epilepsies. In the present study, we are trying to find out the current trend in the prescription pattern of ASD with the clinical profile of epilepsy in a tertiary care center.

Materials and Methods: Patients with Epilepsy who attended Neurology OPD in a tertiary care center in Rajasthan were enrolled between October 2017 to August 2020. Demographic variables including age, gender, type and description of seizures, neurological examination and details of the drugs prescribed, and cost were noted.

Results: Out of the 520 patients, 65% of patients had focal seizures, of which 54% had focal seizures with secondary generalization. About 51% of the patients were given monotherapy and 49% were given polytherapy. There was an inclination towards the prescription of newer ASD as compared to older ASDs with levetiracetam (26.92%) being the most commonly prescribed ASD in the monotherapy group and Sodium valproate or Levetiracetam with Clobazam were most commonly prescribed in 2 drug combination. The average cost of drug per prescription was between 500-1000 INR in 42% of cases, with Newer ASDs is much costlier in comparison to older ASDs.

Conclusion: This study documented a rising trend in newer ASD prescriptions with preference for monotherapy over polytherapy.

Keywords: Antiseizure drugs, Epilepsy, Prescription pattern

INTRODUCTION

Epilepsy is most widely recognized chronic neurologic problems, influencing nearly 70 million individuals worldwide. Despite of being a global disease, it has an unequal distribution, and about 80% of the affected individuals reside in developing countries[1].

Despite the current availability of different antiseizuredrugs (ASDs) globally, around 1/3rd patients with epilepsy could not achieve remission while on treatment[2]. In drug resistant epilepsy patients, an increasing trend has been documented in Pharmaco-epidimeological studies about use of ASDs[3].

In majority of patient selection of appropriate ASD is a limiting factor. As nowadays a significant amount of ASDs is available with different mechanisms of action, pharmacokinetics, efficacy and tolerability; therefore the choice for the right treatment is often challenging. The drug characteristic, the epileptic syndrome, seizure types and the patient's profile need to be taken into consideration before prescribing. In clinical practice monotherapy is much more desirable than polytherapy[4].

Variations have been documented in prescription of antiepileptic drugs in developed and developing countries[5]. Newer ASD has changed prescription pattern in India as well as worldwide and it make difficult for choosing appropriate drugs for different type of epilepsies.

Evidence exist in support of different treatment strategies in different groups especially old age and childbearing women[6]. The direct applicability of these regimens will be a greater issue in India due to higher cost

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of newer ASD and lack of medical insurances[5]. Thus in present study we are trying to find out prescription pattern of ASD in a tertiary care center and to the best of our knowledge very few studies have been conducted in India[5] which illuminates us on this matter.

MATERIALS AND METHODS

The present study is cross sectional observational study conducted by department of neurology in a tertiary care hospital attached to a Medical College in Rajasthan, India after receiving Institutional ethical committee approval. The study was conducted over the period of 3 years (from October 2017, to August 2020) in which all epileptic patients attending OPD and devoid of any other comorbid medical conditions like hypertension, metabolic disorders and renal disorders were included in the study.

Written Informed consent was taken from all the participants. Details of all the patients were captured in semi structured proforma which encompasses all the details regarding demographic profile, neurological examination and neuroimaging of patient, type of seizure (as per ILAE 2017 classification[7]), details of ASD prescribed, loss of the salary per visit and cost of the antiepileptic drugs.

Data thus compiled were analyzed further and quantitative data were analyzed by mean and standard deviation and qualitative data were analyzed by percentage and proportions.

RESULTS

Table1: Demographic data of patient with epilepsy

S. No.	Parameters	Number (%)
1	Mean Age ± SD	24.30 ± 12.7
	Median age (Range)	21(4-78)
2	**Gender**	
	Male (%)	276(53.07%)
	Female (%)	244(46.93%)
3.	**Domicile**	
	Rural (%)	359(69.03%)
	Urban (%)	161(30.97%)

A total of 520 patients with epilepsy were analyzed in his study. There was male preponderance (male – 53 % and female – 47 %) with a male to female ratio of 1.1:1. The mean age of patients was 24.30±12.7 years and median age was 21 years. Person with epilepsy belonged to rural areas (n= 359, 69.03%).

Table 2: Clinical Data of patients with epilepsy

S. No.	Clinical Variable	No. of patients
1	**Type of Seizure**	
	Focal Aware	22(4.2 %)
	Focal Impaired Awareness	36(6.9 %)
	Focal with secondary Generalization	281 (54.03 %)
	Generalized	181(34.80%)
2	**Associated with***	
	Tongue Bite	312(60%)
	Incontinence	156(30%)
	Loss of consciousness	432(83.07%)
	Abnormal Behavior	99(19.03%)
	*More than one symptom in one patient so total is above 520.	
3.	**Aura**	
	Present	172(33.07%)
	Absent	348(66.93%)
4.	**Postictal State**	
	Present	400(76.93%)
	Absent	120(23.07%)
5.	**Precipitating Factor**	
	Sleep Deprivation	114(21.92%)
	TV	6(1.15%)
	Physical Exertion	16(3.08%)
	Acute Stress	104(20%)
	Non Compliance	42(8.08%)
	Menstruation	16(3.08%)
	Other	68(13.08%)*
	None	154(29.62%)
6.	**Frequency of Attack**	
	Weekly	52(10%)
	Monthly	125(24.03%)
	Quarterly	83(15.96%)
	Yearly	62(11.92%)
	>1Year	198(38.07%)
7.	**Diurnal Variation**	
	Night	62(11.93%)
	Day	166(31.92%)
	Anytime	292(56.15%)
8.	**Substance use history**	
	Yes	47(9.03%)
	No	473(90.97%)

9.	**Birth History**	
	Premature	5(0.96%)
	Normal(without complication)	510(98.08%)
	Postmature	0(0%)
	Birth Asphyxia	5(0.96%)
10.	**Family History**	
	Not Significant	478(91.92%)
	Epilepsy	36(6.92%)
	Intellectual Disability	6(1.16%)

While looking at clinical data majority of patients (65.13%) had Focal seizure, among which 54 % patients had focal seizure with secondary Generalization followed by generalized seizure in 34.8%(n=181) cases, which includes Generalized tonic, Generalized clonic, Generalized tonic clonic, Absence (1.92% cases) and Generalized Myoclonic seizures. Loss of consciousness was common feature associated with seizures in around 432 patients (83.07%) and about 33.07% (n=172) had Aura. Seventy seven percent patients (n=400) had postictal confusion and headache. Majority of patients (n=198) were seizure free for more than a year. After going into the detailed history 6.9% patients (n = 36) had family history of epilepsy in one of the relatives.

Table 3: Neurological examination and Lab investigation

S. No.	Name of Neurological examination/Investigation	No. of patients (%)
1	**Higher Mental Function (HMF)**	
	Normal	494(95%)
	Abnormal	26(5%)
2	**Speech**	
	Normal	494(95%)
	Abnormal	26(5%)
3	**Motor System**	
	a. Upper Limb	
	Normal	426(81.92%)
	Abnormal	94(18.08%)
	b. **Lower Limb**	
	Normal	494(95%)
	Abnormal	26(5%)
4.	**EEG**	
	Normal	369(70.96%)
	Abnormal	151(29.04%)
5.	**CT Scan/ MRI Brain**	
	Normal	437(84.03%)
	Abnormal	83(15.97%)

Focal neurological deficit in the form of hemiparesis, hemiplegia, monoparesis, monoplegia, cranial nerve palsies and slurring of speech was reported among patients with HMF and Speech was abnormal in 26 patients (5%) and motor neurodefecit in upper limb and lower limbs was depicted in 18% and 5% patients respectively. Electroencephalography was abnormal in 29% patients and Neuroimaging was abnormal in 15% patients.

Table 4: Anti Seizure drug regimes prescribed

REGIME	Name of Drug	No.of patient (%)
1 Drug	Carbamazepine (CBZ)	47(9.03%)
	Phenytoin (PHT)	16(3.07%)
	Levetiracetam (LEV)	140(26.92%)
	Sodium Valproate (VAL)	62(11.92%)
	TOTAL	**265 (50.96 %)**
2 Drugs	PHT + CLO	10 (1.92%)
	PHT + LEV	26 (5%)
	PHT + PHB	4 (0.76%)
	VAL + OCB	5(0.96%)
	VAL + PHB	10(1.92%)
	VAL + CLO	47(9.03%)
	LEV + CLO	47 (9.03%)
	LEV + VAL	21(4.03%)
	LEV + OCB	10(1.92%)
	OCB + CLO	6(1.15%)
	TOTAL	**186 (35.8%)**
3 Drugs	CBZ + LEV + CLO	10(1.92%)
	CBZ + LEV + VAL	5(0.96%)
	PHT + LEV + CBZ	6(1.15%)
	PHT + LEV + CLO	5(0.96%)
	PHT + CBZ + PHB	6(1.15%)
	PHT + VAL + PHB	5(0.96%)
	PHT + PHB + LEV	6(1.15%)
	VAL + LAC + LEV	5(0.96%)
	VAL + LEV + CLO	21(4.03%)
	TOTAL	**69 (13.2 %)**

Abbreviation- Carbamazepine (CBZ), Phenytoin (PHT), Levetricetam (LEV), Sodium Valproate (VAL), Clobazam (CLO), Phenobarbitone (PHB)

Half of the patients (50.96 %) were being managed on a single ASD treatment regimen. Of which, Levetiracetam was the most frequent drug (26.92%) followed by Sodium Valproate (11.92 %) and Carbamazepine (9.03 %) respectively. The remaining half

of the patients were on polytherapy of ASDs. Of which, Valproate with Clobazam and Levetiracetam with Clobazamwere the most prescribed 2 drugs combinations (9.03%) while Valproate, Clobazam with Levetiracetam topped the list of 3 drugs combinations.

Table 5: Average Loss of Salary during each doctor visit

S .No.	Range of loss of salary per visit (INR)	No. Of patients(n=520)
1	⩽500INR	156(30%)
2	501INR-1000INR	234(45%)
3	1001 INR-5000INR	99(19.03%)
4	>5001 INR	31(5.96%)

People spent more than three hours on the average doctor's visit, which means they spent three hours not doing work and sometimes they even take full day leave. In our study, average loss of salary during each visit is around 500-1000 Rs. in 45 % (n=234) patients.

Table 6: Cost of antiepileptic drugs per month

S. No.	Cost of antiepileptic drug per month (INR)	No. of patients (N=520)
1	50 INR-500 INR	130(25%)
2	501-1000 INR	218(41.92%)
3	1001-2000INR	135(25.96%)
4	2001-3000 INR	26(5%)
5.	>3000 INR	11(2.11%)

Table 7: Cost analysis

REGIME	Name of Drug	Maximum cost (per month)-INR	Minimum cost (per month)-INR
1 Drug	CBZ	2000	150
	PHT	600	60
	LEV	2000	350
	VAL	2200	300
2 Drugs	PHT + CLO	700	300
	PHT + LEV	1200	400
	PHT + PHB	300	60
	VAL + OCB	1700	900
	VAL + PHB	1500	600
	VAL + CLO	2500	850
	LEV + CLO	2500	800
	LEV + VAL	3000	1000
	LEV + OCB	2000	1000
	OCB + CLO	1700	950
3 Drugs	CBZ + LEV + CLO	2800	300
	CBZ + LEV + VAL	3400	600
	PHT + LEV + CBZ	2500	750
	PHT + LEV + CLO	1000	450
	PHT + CBZ + PHB	1704	850
	PHT + VAL + PHB	1200	500
	PHT + PHB + LEV	980	535
	VAL + LAC + LEV	3600	1200
	VAL + LEV + CLO	2500	1100

Abbreviation- Carbamazepine (CBZ), Phenytoin (PHT), Levetricetam (LEV), Sodium Valproate (VAL), Clobazam (CLO), Phenobarbitone (PHB)

In table 6 and 7, the prices of various anti seizure drugs available in the Indian market and produced by different pharmaceutical companies were analyzed.

The average cost of Anti seizure drugs per prescription was between 500-1000 INR for 42% cases (n=218), 1001-2000 INR for one- fourth patients (n=135) and 50- 500 INR for another one-fourth patients. Minimum and maximum average cost in rupees (INR) per prescription of the monotherapy drugs (most commonly prescribed - levetiracetam and valproic acid) was around 300-2000 INR respectively, and that of polytherapy is given in table 8.

DISCUSSION

A total of 520 Patients with epilepsy were enrolled in this study. The median age of onset of seizure

was 21 years (range, 4 years to 78 years) with mean age of patients was 24.30±12.7 years, which is in consistent with our previous studies[8,9]. Majority of previous studies from India reported a higher prevalence during the 2nd decade[7-,10] while few others reported a bimodal distribution of epilepsy incidence with peaks during early childhood and 2nd during later age of life at their 70s and 80s[10,11].

Our study reported, male preponderance with a male to female ratio of 1.1:1 which was consistent with other studies done in last several years[8-10]. This difference is usually attributed to male's greater exposure to risk factors for Symptomatic localization-related seizures[12] and comparatively higher mortality among female children due to poor care.

Majority of patients in our study belonged to rural population (around 69%) which is similar to the other several studies[10,11]. The possible reasons for this difference could be because of obvious fact that rural population constitutes 63 % of the Indian population[13], limited health care facilities, delivery injuries, malnutrition and several other factors.

Sixty five percent of patients had focal seizures and 35 % had generalized seizures. Subclassification of Focal seizures revealed Focal Aware seizures in 4.2 % of the cases, Focal Impaired Awareness seizures in 6.9% and Focal with secondary Generalization seziuresin 54 % of the cases. Tonic-clonic seizures were the most common type of generalized seizures with absence seizures were seen in 2% of the cases. It was similar to the other studies done in various parts of world[14-16].

In our study 33 % of the patients had aura, which are typically associated with focal epilepsy but a substantial proportion has been reported with generalized epilepsy also. This was also reported in other previous studies[17]. Loss of consciousness was common feature, which could be due to the fact that abnormal *decreased* activity in bilateral fronto-parietal association networks may impair consciousness in complex partial seizures, while abnormal *increased* activity in these same networks may impair consciousness in generalized tonic- clonic seizures[18,19]. Seventy seven percent patients had postictal confusion and headache.

The availability of several ASDs have drastically improved the seizure control in patients with epilepsy. That's why about half of patients in our study were seizure free for a year or more. A positive family history was found in 6.9 % of patients in our study as compared to 7.2% to 32% in various other studies[20,21]. The familial aggregation of disease may be explained by shared genetics and exposure to similar environmental factors .

Epilepsy is often associated with various cognitive, language, motor, sensory and behavioral impairments which may be of variable duration[22]. In our study, 5% patient had cognitive and language impairment with motor neurodefecit in upper limb and lower limbs was 18% and 5% patients respectively.

Among the distribution of ASD treatment regimens, about half of patients were on monotherapy and another half on combination therapy. LEV, VPA, CBZ and PHT were the most regularly prescribed ASDs in monotherapy regimens. In this study, there was an inclination towards the prescription of newer ASD as compared to older ASDs, as studies conducted so far had showed levetiracetam as a suitable option for initial monotherapy in newly diagnosed epilepsy, especially in women of child bearing age with better tolerability and improved compliance among patients due to longer treatment withdrawal time[23,24].

As per Indian rules on epilepsy, treatment ought to be started with one ASD without changing the brand. In the event if the patient doesn't react to monotherapy, then, at that point the antiepileptic can be changed and the dose of ASD can be gradually increases till seizure controlled is accomplished. Combination therapy to be considered after two endeavors at monotherapy have failed[25]. Valproate or Levetriacetam with Clobazam were the two most commonly prescribed drugs combinations. This could be due to fact that clobazam is safe and well tolerated add-on antiseizure drug, which is effective in both types of seizures *i.e.* generalized as well as focal[26]. Other ASD combinations which were prescribed in our study were first generation and second generation ASDs (like, phenytoin and levetriacetam or valproate and levetriacetam), those with differing mechanisms of action which is proven to be more effective than polytherapy with similar mechanisms of action[27,28]. In our study, >2 drugs were given to a 13.2 % of patients with combination of VAL, LEV and CLO as most commonly prescribed among all. “Third generation” ASDs (eglacosamide) was added as adjunctive treatment in cases with refractory seizures, as it has synergistic interaction with various AEDs, without additional adverse effects[29].

In the present study, the cost of daily dose of the most commonly prescribed brand of both older and newer ASDs was noted. Overall Newer AEDs is much costlier in comparison to older AEDs which was in concordance with the finding of another studies[5,30]. In our study, the total cost of monthly treatment of levetiracetam with older drug like valproic acid as monotherapy was found to be equivalent. Average monthly cost of ASD vary per prescription, due to difference between cost of generic ASD & different brands of ASDs, drug dose of same ASD and combination prescribed.

CONCLUSION

The Clinician selection of ASD depends upon the drug efficacy, tolerability, seizure type, patient's profileand affordability; therefore the choice for the right treatment is often challenging. This study documented a rising trend in newer ASD prescription, monotherapy should always be preferred over polytherapy.

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